Drug-induced skin reactions or drug eruption is a general term for eruptions in the skin and mucosa induced by a drug or its metabolites. Drug-induced skin reactions show various morphologies. Maculopapular or morbilliform eruptions may be the most common of all cutaneous drug reactions. It is also known that cutaneous drug reactions present the specific morphological patterns. Clinical images are available in hardcopy only.

A. Drug-induced skin reactions

Outline

- Drug-induced skin reaction or drug eruption is a general term for eruptions in the skin and mucosa induced by a drug or its metabolites.
- Drug-induced skin reactions show various morphologies.

General information

Maculopapular or morbilliform eruptions may be the most common of all cutaneous drug reactions. It is also known that cutaneous drug reactions present the specific morphological patterns. (Figs. 10.1-1 and 10.1-2). In diagnosing skin diseases, it is essential to consider drugs as a possible cause of any eruption, because drug eruptions can take the form of any skin lesion. Drug eruptions may be accompanied by general symptoms including fatigue, fever, lymph node enlargement, dysfunction of the internal organs such as liver, kidneys or bone marrow, hypotension and shock.

Classification, Pathogenesis

Drug eruptions are roughly divided into immunologic and non-immunologic. The pathogenesis is unclear in some cases. The eruptions are often classified by their clinical features (Table 10.1, Figs. 10.2-1 and 10.2-2).

Treatment

It is essential to discontinue the causative medication. In serious cases, such as anaphylactic shock, systemic management using steroids in large doses including antihistamines, epinephrines, and steroids in large doses, including by pulse therapy.

a. Classification of drug eruptions by pathogenesis (Table 10.2)

1. Immunologic drug reactions

A drug or the complex of a drug and a serum protein becomes
antigenic, causing a drug eruption that results from immunological processes. That is, a drug eruption occurs in specific individuals whose antibodies and lymphocytes react against specific antigens. Although type I, II, III, and IV hypersensitivities are thought to cause drug eruptions (Coombs and Gell classification), the details of the pathogeneses are unknown.

**IgE mediated type I allergy**: Within 2 hours after exposure to an antigen (e.g., penicillin or some NSAIDs), urticaria or anaphylactic shock occurs.

**Type II allergy**: Complements are activated by an antigenic drug that connects with tissues, resulting in hemolytic anemia and thrombocytopenia. It is observed in some cases of purpura-like eruptions.

**Immune complex-associated type III allergy**: Immune complex deposits in tissues, causing disorders. Vasculitic eruptions are thought to be caused by this mechanism.

**Type IV allergy**: A delayed hypersensitivity reaction is induced by T cells that have been sensitized to drug antigens. It is known that many types of drug eruptions, such eczema-like eruptions, are produced by type IV allergy or by T-cell mechanisms that resemble type IV allergy.

### Table 10.1 Drug-induced skin reactions and their typical causative drugs.

<table>
<thead>
<tr>
<th>Type of eruption in drug-induced reactions</th>
<th>Causative drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular</td>
<td>Iohexol, iomeprol, ampicillin, amoxicillin, carbamazepine, mexiletine, tiopronin</td>
</tr>
<tr>
<td>Photosensitive</td>
<td>Sparfloxacin, fleroxacin, iomefl oxacin, piroxicam, ampiroxicam, griseofulvin, mequitazine, ketoprofen</td>
</tr>
<tr>
<td>Fixed-drug eruption</td>
<td>Allylisopropylacetyl urea, melenamic acid, ethanzamide, barbital, minocycline, sulfamethoxazole, piroxicam, fluorouracil</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Iohexol, carbamazepine, amoxicillin, tiopronin, phenytoin, diltiazem, mexiletine</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>Tiopronin, captopril, interferon α, cyanamide, oxatrimide</td>
</tr>
<tr>
<td>Urticarial</td>
<td>Cefaclor, minocycline, iohexol, aspirin, cetrazate, melenamic acid</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis (TEN)</td>
<td>Cefzonom, penicillin, phenobarbital, chloromezanone, carbamazepine, methazolamide, acetaminophen, allopi rulin, diclofenac</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Penicillin, chlorpromazine, sulfamethoxazole, sodium aurothiomalate, phenytoin</td>
</tr>
<tr>
<td>Erythodermic</td>
<td>Carbamazepine, sodium aurothiomalate, cyanamide, allopi rulin, ampicillin</td>
</tr>
<tr>
<td>Vesiculo-bullous</td>
<td>D-penicillamine, tiopronin, captopril, bucillamine, alacepril</td>
</tr>
<tr>
<td>Eczematous</td>
<td>Penicillin, chlorpromazine, chloro thiiazide, promethazine</td>
</tr>
<tr>
<td>Purpuric</td>
<td>Sodium aurothiomalate, sulfamethoxazole, penicillin, aspirin</td>
</tr>
</tbody>
</table>

Drug-induced skin reactions without an immunologic pathogenesis may affect anyone, regardless of whether there has been sensitization. The pathogenesis of drug-induced skin reactions can also be classified pharmacokinetically.

**Pharmacologic effects**: Drug-induced skin reactions may be produced by essential pharmacological action of the drug. Hair loss
caused by anticancer agents and exfoliation in palms and soles caused by retinoids are examples. Accumulation: A drug accumulates in the skin or mucous membranes from prolonged use (arsenic melanoderma and argyria are examples of accumulation disorders). Drug interaction: One drug may inhibit another drug’s metabolism or excretion, or it may influence protein binding, leading to the same symptoms as those in drug overdose. Specific condition of patients: Inherited enzyme deficiency may cause drug reactions; excessive reaction occurs against a minute amount of drug (intolerance). An unexpected action of the drug is caused (idiosyncrasy).

### c. Methods of identifying the causative drug

History is taken on drug-induced skin reactions and on exacerbation or remission of eruptions influenced by use or discontinuation of a drug. If the eruption is suspected to be drug-induced reactions, tests listed below are conducted for identification (Chapter 5).

1. Skin test (scratch test, prick test, intradermal test)
2. Patch test
3. Drug lymphocyte stimulation test (DLST)
4. Rechallenge test (absolutely contraindicated in severe forms of drug reactions)
Fixed drug eruptions (FDEs) are eruptions that recur at the same site each time the same drug is administered. They frequently occur at mucocutaneous junctions.

FDEs frequently occur at mucocutaneous junctions, such as in the perioral area, lips and genitalia, and in the extremities. They are characterized by a single or a few sharply demarcated red or purple patches (Fig. 10.3), with a diameter of 1 cm to 10 cm. Multiple patches may also occur. They may appear as blistering or erosion. Itching and pain are common. The lesions appear several minutes to several hours after the administration of the causative drug. They heal in 2 to 5 weeks, leaving pigmentation. If the same drug was administered repeatedly, the dark brown pigmentation intensifies from inflammation in the basal layer, and subsequent melanin deposition in the dermis (post-inflammatory pigmentation).

FDEs are caused by the activation of cytotoxic T lymphocytes in the basal layer by drugs. Common causative drugs are NSAIDs, tetracyclines, sulfa drugs, phenacetin, hypnogenics and food additives.

FDEs are diagnosed by detailed history-taking on drugs and the course of the eruptions. A patch test performed on the site where an eruption has occurred is positive with high frequency; it is diagnostically meaningful.

The causative drug should be discontinued.

There are several specific clinical types of drug-induced skin reactions that may lead to death. Toxic epidermal necrolysis (TEN) has the highest mortality (30-35%); Stevens-Johnson syndrome and transitional forms correspond to the same syndrome, but with less extensive skin detachment and a lower mortality (5-15%).

Hypersensitivity syndrome, sometimes called drug-induced
hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS), has a mortality of about 10% or less.

1) Toxic epidermal necrolysis (TEN)

**Synonym:** Lyell’s syndrome

**Clinical features, Classification**

Toxic epidermal necrolysis (TEN) is one of the severest drug eruptions. It is accompanied by fever, and erythema and blistering on the whole body surface. It leads to marked epidermal necrosis and exfoliation (Figs. 10.4-1 and 10.4-2). It is closely related to Stevens-Johnson syndrome (SJS) (Fig. 10.5). TEN is classified into several types according to the clinical course.

**TEN developing from SJS:** Most cases of TEN develop from SJS. Vaguely outlined, small, dark red edematous erythema sparsely appear on the whole body and gradually spread. They subsequently increase and form blisters and erosion. Typical primary lesions are characterized by so-called target lesions with dusky centers. Severe erosion develops in the oral mucosa, and systemic symptoms such as fever and fatigue are seen. SJS is characterized by the transformation of erythema into blistering...
and erosion with dark red patches at the periphery (Chapter 9).

**Rapid extensive type:** This is the type that Lyell first reported. Two to 3 days after intake of the causative drug, erythroderma and extensive erosions occur on the whole body surface without preceding macules, and the skin exfoliates easily; it is similar to a large burn (second-degree). This type accounts for several percent of all TEN cases (Fig. 10.6).

**Pathogenesis**

It is widely accepted that the cellular functions of cytotoxic T cells are abnormally enhanced by certain drugs, including sulfa drugs, penicillin, barbituric acids, aspirins, pyrazolone drugs, and anticonvulsants, and epidermal necrosis and subepidermal separation occurs as a result. Fas-Fas ligands, which induce apoptosis in epidermal cells, are thought to be involved in the occurrence of TEN.

**Treatment**

Use of the causative drug should be discontinued immediately. Systemic glucocorticosteroids in high doses, including pulse therapy, are widely known to be useful in the early stages of TEN, but not in the late stage of the disease course. Intensive care with topical treatment and body fluid management similar to the patients with burns are essential. Plasma exchange may be conducted, and large doses of immunoglobulins may also be applied. The causative drug must not be readministered.

2) Drug-induced hypersensitivity syndrome

Synonyms: Drug hypersensitivity syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS)

There is still controversy on the naming of this newly proposed concept of the disease condition, but each different disease name may indicate the same or similar condition which is induced by drug. Drug-induced hypersensitivity syndrome (DIHS) is proposed by a group of Japanese dermatologists which holds that skin lesions are caused by a combination of drug allergy and reactivated latent viral infection, specifically human herpes virus 6 (HHV 6) infection. Two to 6 weeks after administration of a specific drug, fever
and generalized maculopapular erythema occurs (Fig. 10.7), which results in erythroderma in some cases. Enlargement of superficial lymph nodes, liver dysfunction and hematological abnormalities (leukocytosis, appearance of atypical lymphocytes, increase of eosinophils) occur. There is also a report that suggests the involvement of cytomegalovirus and human herpes virus (HHV-7) in DIHS. The diagnostic criteria are listed in Table 10.3 (also refer to Chapter 23 for viral infections).

Drug reaction with eosinophilia and systemic symptoms (DRESS) is thought to be the same or similar syndrome, which is mainly used by European dermatologists group. The important point is that dermatologists should be aware of these systemic drug-induced reactions in association with marked eruption, and that routine laboratory examination is necessary when a drug eruption is suspected.

The treatements include systemic corticosteroid and termination of the causative drug.

### B. GVHD and viral eruptions

| 1. Graft-versus-host disease (GVHD) |

**Outline**

- After bone marrow transplantation, other organ transplantation or transfusion, donor lymphocytes are stimulated by major and/or minor histocompatibility locus antigens and subsequently target host tissues for cytotoxic damage.
- The skin, intestinal tract and liver are the main affected organs.
- In acute GVHD, erythematous macules occurs on the palms and spread over the whole body. In chronic GVHD, lichen-planus-like and scleroderma-like eruptions are found.
**Definition, Pathogenesis**

When donor-derived blood cells circulate in the patient’s skin after transplantation, the immunocompetent donor, T cells, may recognize the foreign host's histocompatibility locus antigens (HLA). Subsequently, an immune reaction against the host's organs occurs. It may also be caused by general blood transfusions.

**Classification**

As shown in Table 10.4, graft-versus-host disease (GVHD) is categorized by the onset. The skin, digestive tract, and liver are the main organs affected, and the symptoms are mainly seen in those organs. Post-transfusion GVHD occurs about 10 days after a transfusion and has a poor prognosis. Congenital GVHD occurs after birth, and intractable dermatitis, diarrhea, opportunistic infections, and disturbance in growth are caused by lymphocytes transferred from the mother.

**Clinical features**

**Acute GVHD:** In most cases, 10 to 30 days after a graft, edematous erythema appears on the extremities and trunk. It may be accompanied by slight itching. In severe cases, the eruptions coalesce and may develop into erythroderma, blistering, or erosion (Figs. 10.8-1 and 10.8-2). Symptoms of acute GVHD may remain longer even after the first 100 days or more after transplantation, as a result of recent improvements in immunosuppressive drugs.

**Chronic GVHD:** This includes lichenoid forms and sclerodermoid forms. The lichenoid forms multiple purplish-red plaques resembling lichen planus, and the sclerodermoid forms sclerotic lesions resembling scleroderma.

The severity of GVHD is classified according to the severity of the skin lesions and other organ disorders (Table 10.5).

**Pathology**

GVHD pathologically presents a lichenoid reaction. Intradermal lymphocyte infiltration, necrosis of the epidermal cells, and

**Table 10.4 Classification of graft-versus-host disease (GVHD).**

<table>
<thead>
<tr>
<th>Type of GVHD</th>
<th>Duration after transplantation/transfusion</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>7 to 14 days</td>
<td>Fever, diarrhea, erythrodermic skin eruption, pulmonary edema, heart failure</td>
</tr>
<tr>
<td>Acute</td>
<td>Up to 100 days</td>
<td>Triad (fever, diarrhea and liver dysfunction). Poorly demarcated erythema seen on the face and palmoplantar area. In severe cases, TEN and erythroderma.</td>
</tr>
<tr>
<td>Chronic</td>
<td>More than 100 days</td>
<td>Various skin lesions like those in collagen diseases and lichen planus. Liver dysfunction, oral symptoms, ocular symptoms.</td>
</tr>
<tr>
<td>Transfusion-associated</td>
<td>About 10 days</td>
<td>Resemble those of hyperacute GVHD. Prognosis is poor.</td>
</tr>
</tbody>
</table>

**Clinical images are available in hardcopy only.**

**Fig. 10.8-1 Acute graft-versus-host disease (GVHD).**
a: Diffuse erythema on the back after bone marrow transplantation. Differential diagnosis from drug eruption is almost impossible clinically. b, c: Severe acute GVHD. Severe exfoliation similar to toxic epidermal necrolysis is seen.
vacuolar degeneration of the basal cell layer are found (Chapter 2). The number of Langerhans cells decreases.

GVHD needs to be differentiated from drug-induced skin reactions, eruptions of peripheral lymphocyte recovery accompanying a graft (generally 10 to 14 days after transplant), and viral infections.

Immunosuppressants (cyclosporine, tacrolimus, azathioprine, cyclophosphamide) and steroids are administered orally. Post-transfusion GVHD can be prevented by irradiating the blood to be transfused.

**Differential diagnosis**

GVHD needs to be differentiated from drug-induced skin reactions, eruptions of peripheral lymphocyte recovery accompanying a graft (generally 10 to 14 days after transplant), and viral infections.

**Treatment**

Immunosuppressants (cyclosporine, tacrolimus, azathioprine, cyclophosphamide) and steroids are administered orally. Post-transfusion GVHD can be prevented by irradiating the blood to be transfused.

**2. Viral eruption**

When maculopapular erythema appear abruptly on the whole body of a febrile patient who has been administered NSAIDs or any other medicine for that condition, a drug reaction or a viral infection are the two most likely diagnoses. In those cases, differentiation between drug-induced eruption and viral eruption is often difficult, even with thorough examination. Drug-induced hypersensitivity syndrome (DIHS) is thought to be caused by causative drug as well as re-activation of latent viral infection. Refer to Chapter 23 for details on viral infections.